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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,883	12/21/2000	Hans-Ulrich Demuth	20784-5	1277

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	14

DATE MAILED: 06/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/745,883	Applicant(s) DEMUTH ET AL.	
	Examiner Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because it lists the foreign application DE 19828114.5 and PCT/EP99/04381 under 35 U.S.C. § 120 and/or 121, it should claim foreign priority benefits under 35 U.S.C. § 119(a)-(d).

Election/Restrictions

2. Applicant's election with traverse of Group II, claims 1-8 and 11-14, and diabetes as the elected disease in Paper No. 13 is acknowledged. The traversal is on the ground(s) that there is no serious burden to include Group I (claims 9 and 10), which is a method of making. The argument is found persuasive, thus, claims 1-14 will be examined. Regarding the diseases, applicants argue that all the diseases of claim 13 have a common etiology, which is the mismanagement of DP IV activity. The argument is not found persuasive because each disease, which has different cause, uses different drug and has different outcome for the treatment, is considered patentably distinct. Therefore, claims 1-14 and diabetes are examined. The requirement is still deemed proper and is therefore made FINAL.

Informalities

The disclosure is objected to because of the following informalities:

3. The specification uses the brackets [...] in the text, e.g., "[see Demuth,.....1995, 1-37]" at page 1, lines 14-16. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be

printed in the published patent. Applicant has used "[...]" in such a manner that appears the instant brackets would indicate deleted material and is thus, confusing as to whether the reference in the bracket would be included in the specification. Appropriate correction is required.

4. The specification indicates H-Val-Pro-$CH_2(N^+C_5H_5)$ has a short half life of 13.3 min in Table 1 (page 18), however, it also indicates it is stable over 24 hours under the same conditions (page 18, lines 5-7). Appropriate correction is required.

Claim Objections

5. Claim 1 is objected to because of the use of "A is an amino acid B is a chemical..." A comma "," should be inserted after the phrase "A is an amino acid".

6. Claim 4 is objected to because of the use of the term "consisting of is Ile-Thia". The word "is" should be deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11-13 are directed to a method of treating disorders such as diabetes mellitus in mammals by modulating the DP IV enzymatic activity comprising administering the compound

A-B-C, where C is an unstable inhibitor of DP IV. The specification indicates the tetrapeptide such as Gly-Pro-Val-Pro-$CH_2(N^+C_5H_5)\cdot Cl^-$ is stable in buffer and the dipeptide inhibitor Val-Pro-$CH_2(N^+C_5H_5)$ is only released when DP IV is added. Due to its delayed release, the tetrapeptide has a prolonged activity and inhibits DP IV at a much lower concentration as compared the dipeptide inhibitor (page 18, line 9-page 19, line 2; Fig. 8). The specification also indicates the compounds containing the unstable inhibitors of DP IV can be used for treating metabolic disorders associated with diabetes mellitus, and the masked inhibitor is more effective than the non-masked inhibitors because the masked compound produces a marked improvement in glucose tolerance in Wistar rats (page 3, lines 15-21). However, the specification has not demonstrated the use of the tetrapeptide Gly-Pro-Val-Pro-$CH_2(N^+C_5H_5)\cdot Cl^-$ in treating diabetes mellitus, nor has indicated the treating conditions such as the dose, the method of administration and the effect of the compound. There is no disclosure indicating the make and use of any other compounds containing an unstable inhibitor of DP IV in the treatment. Without guidance on the treating conditions for diabetes mellitus using compounds containing an unstable inhibitor of DP IV, one skilled in the art would not know how to treat the disease. The lack of description of the use of compounds containing an unstable inhibitor of DP IV in the treatment of diabetes mellitus as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-3, 5, 6 and 8-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5, 6 and 8-13 are indefinite because of the use of the term "C is an unstable inhibitor of DP IV". The term "C is an unstable inhibitor of DP IV" renders the claim indefinite, it is unclear what compound is intended as to "unstable inhibitor of DP IV", and how the unstable inhibitor is defined. Claims 2-3, 5, 6, 8, 10, 12 and 13 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

9. Claims 2 and 4 are indefinite because of the use of the term "consisting of.....or ...". Note that Markush group is recited in the claim, the phrase "consisting of.....and...." should be used. Claim 4 is also indefinite because of the use of the terms "Thia" and "Pyr", it is not clear what the term means. A full chemical name should be indicated.

10. Claims 4, 7 and 14 are indefinite because of the use of the term "dipeptide derivative", "dipeptidyl alkyl ketone derivative" or "a fluoro alkyl ketone derivative". The term "dipeptide derivative", "dipeptidyl alkyl ketone derivative" or "a fluoro alkyl ketone derivative" renders the claim indefinite, it is unclear what compound is as to "derivative", and how different the derivative is from the parent compound.

11. Claims 9 and 10 are indefinite because they lack essential steps as claimed in the method of preparing a pharmaceutical composition. The omitted step is the preparation of the pharmaceutical composition from the compound of A-B-C. Claim 10 is included in the rejection

because it is dependent on a rejected claim and does not correct the deficiency of the claim from which it depends.

12. Claims 11-13 are indefinite because they lack essential steps as claimed in the method of treating disorders. The omitted steps are: the effective amount of the compound used, the method of administration and the outcome for the treatment. Claims 12 and 13 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend. Claims 11 and 12 are also indefinite as to "disorders" or 'metabolic disorders", it is not clear what disorder is intended.

13. Claim 13 is indefinite because the claim contains non-elected diseases.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-3, 5 and 8-12 are rejected under 35 U.S.C. 102(b) as anticipated by Bachovchin *et al.* (WO 93/08259).

Bachovchin *et al.* disclose the dipeptides having boroPro moiety as DP IV inhibitors are relatively unstable, but the tetrapeptides such as X-Pro-Y-boroPro, where X and Y are chosen from any amino acid including Pro, function as DP IV inhibitors because the dipeptide portion is a substrate of DP IV and the final product is the dipeptide inhibitor Y-boroPro (pages 2, lines 18-35; claims 1-3). The final boroPro peptides are obtained as salts by removing the protecting group with anhydrous HCl, HBr or trifuoroacetic acid (page 12, lines 19-26; claim 5). The

boroPro peptides can be prepared with a pharmaceutically acceptable carrier and administered orally to a mammal for inhibiting enzymatic activity of DP IV (page 6, line 4-page 7, line 35; page 21, lines 4-6; claims 8-10). The compound can be used for treating various diseases such as autoimmune disease or delaying catabolism of growth releasing factor, where DP IV plays a role (page 21, lines 7-30; claims 11 and 12).

15. Claims 1-3, 5 and 7-11 are rejected under 35 U.S.C. 102(b) as anticipated by Bachovchin *et al.* (WO 95/11689).

Bachovchin *et al.* disclose the dipeptides having boroPro moiety as DP IV inhibitors are relatively unstable, but the tetrapeptides such as X-Pro-Y-boroPro, where X and Y are chosen from any amino acid including Pro, function as DP IV inhibitors because the dipeptide portion is a substrate of DP IV and the final product is the dipeptide inhibitor Y-boroPro (pages 2, lines 16-32; claims 1-3). The final boroPro peptides are obtained as salts by removing the protecting group with anhydrous HCl, HBr or trifuoroacetic acid (page 12, line 30-page 13, line 2; claim 5). The boroPro peptides can be formulated in sustained release form and administered orally to a mammal for blocking DP IV (CD26), thus blocking entry of HIV into CD26-bearing cells (pages 7, line 7-34; claims 8-11). The compounds can be boronates, fluoroalkyl ketones or phosphoramidates (page 8, line 29- page 9, line 5; claim 7).

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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June 10, 2002

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER